

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference D 2398 PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP00/05922	International filing date (day/month/year) 26/06/2000	Priority date (day/month/year) 25/06/1999
International Patent Classification (IPC) or national classification and IPC C12N15/10		
Applicant UNIVERSITÄT ZÜRICH et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 7 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 08/01/2001	Date of completion of this report 05.10.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 -0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Lanzrein, M Telephone No. +49 89 2399 7358 

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/05922

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-38 as originally filed

Claims, No.:

1-22 as originally filed

Drawings, sheets:

1/11-11/11 as originally filed

Sequence listing part of the description, pages:

1-9, filed with the letter of 02.10.2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

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- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 8, 10-13, 15-22 (all partially).

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
 - ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 - ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 - ☒ no international search report has been established for the said claims Nos. 8, 10-13, 15-22 (all partially).
2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
- ☐ the written form has not been furnished or does not comply with the standard.
 - ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

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1. Statement

Novelty (N)	Yes:	Claims	1-22
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-22
Industrial applicability (IA)	Yes:	Claims	1-22
	No:	Claims	

2. Citations and explanations see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/05922

Reference is made to the following documents:

- D1: O'SHEA E K ET AL: 'PEPTIDE 'VELCRO': DESIGN OF A HETERODIMERIC COILED COIL' CURRENT BIOLOGY,GB,CURRENT SCIENCE,, vol. 3, no. 10, 1993, pages 658-667, ISSN: 0960-9822 cited in the application
- D2: YU Y ET AL: 'INVESTIGATION OF ELECTROSTATIC INTERACTIONS IN TWO-STRANDED COILED-COILS THROUGH RESIDUE SHUFFLING' BIOPHYSICAL CHEMISTRY,AMSTERDAM,NL, vol. 59, 16 April 1996 (1996-04-16), pages 299-314, cited in the application
- D3: HODGES R S: 'DE NOVO DESIGN OF ALPHA-HELICAL PROTEINS: BASIC RESEARCH TO MEDICALAPPLICATIONS' BIOCHEMISTRY AND CELL BIOLOGY. BIOCHIMIE ET BIOLOGIE CELLULAIRE,XX,XX, vol. 74, no. 2, 1996, pages 133-154, ISSN: 0829-8211 cited in the application
- D4: ARNDT K M ET AL: 'In-vivo selection of interacting peptide libraries by selectively-infective phages.' FASEB JOURNAL, vol. 11, no. 9, 1997, page A1327 17th International Congress of Biochemistry and Molecular Biology in conjunction with the Annual Meeting of the American Society for Biochemistry and Molecular Biology;San Francisco, California, USA; August 24-29, 1997 ISSN: 0892-6638
- D5: WO 98 34120 A (PELLETIER JOELLE NINA ;REMY INGRID (CA); UNIV MONTREAL (CA); MICHN) 6 August 1998 (1998-08-06) cited in the application

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Parts of claim 8 and appendent claims 10-13, 15-22 have not been searched. The non-searched subject-matter is not subject to the preliminary examination as set forth under Rule 66.1 (e) PCT.

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Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The current application concerns a method for selecting hetero-associating polypeptides. Two peptide libraries are simultaneously expressed in a cell and the hetero-association is selected by reconstitution of the DHFR enzyme. The design of the peptide libraries is based on coiled-coil forming domains of the fos/jun/gcn4 leucine-zipper.

Claims cover the method for identification of peptides as well as the peptides themselves. The specific peptides claimed (e.g. present claims 5, 6) comprise amino acid variations at the e and g positions of the coiled-coil forming heptad motifs.

2. Claims 1-22 appear to be novel over the cited prior art.

3. Claims 1-22 lack inventive step within the meaning of Art. 33 (3) PCT.

- 3.1 Claims 5, 6, 8-22 essentially concern polypeptides capable of hetero-associating. The polypeptide sequences recited in said claims are novel.

However, other hetero-associating peptide pairs have been disclosed in the prior art (D1-D3). For example D1 shows two peptides designed based on studies of fos, jun and gcn4 leucine zippers. Said peptides preferentially form a stable, helical heterodimer (p. 660, right-hand column, 1. paragraph; Fig. 3). D3 and D4 disclose other peptide sequences with similar properties.

In order for the peptides of the present application to be inventive, they must satisfy the criteria of a selection invention. This means the peptides must be distinguished from the known ones by a special technical effect. If there is no such special technical effect or feature which distinguishes the present peptides, the contribution of the application lies only in an arbitrary selection from a large number of possible peptides.

The availability of many sequences in the prior art (D1-D3) in fact shows that the skilled person would find other possible sequences derivable from the jun/fos leucine

zipper or any other known coiled-coil forming pair without exercise of inventive skill. In other words, there is a large number of peptides derivable from jun/fos, illustrated by the fact that this approach was used successfully several times (D1-D4). Therefore, for new peptides obtained by said approach, a special technical effect must be evident in order for inventive step to be acknowledged.

- 3.2 Claims 1-4, 7 concern a method for identification of hetero-associating polypeptides by combining two peptide libraries and selecting for a property caused by the hetero-association.

D4, which is considered the closest prior art document discloses a method for in vivo screening of interacting peptide libraries. Potential coiled-coil forming peptides were randomized at the e and g-positions of the heptad. The two libraries were fused to the N- or C-terminal half of the Genelll bacteriophage protein, which provided a selection-marker for heterodimerization.

Thus, the differences between present claims 1-3, 7 and D4 are the specific peptides recited in said claims.

However, as set forth above, said peptides are not considered inventive and therefore cannot establish inventive step of the method which is known as such.

Claim 4 concerns another selection method using DHFR enzyme reconstitution. However, this feature is known from D5 and thus cannot establish inventive step.